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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/989,728	11/20/2001	Avi J. Ashkenazi	P2730P1C72	2424

35489 7590 10/19/2004

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EXAMINER	
HAMUD, FOZIA M	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 10/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/989,728	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Fozia M Hamud	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-138* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-138* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: _____.

DETAILED ACTION

1. Applicant's preliminary amendment canceling claims 1-118 and adding new claims 119-138, filed on 20 November 2001 is acknowledged.

Thus claims 119-138 are pending and under consideration.

2. ***Priority:***

2a. Based on the information given by Applicants and an inspection of the patent applications, the Examiner has concluded that the subject matter defined in this application is supported by the disclosure in application serial no. 09/941,992 filed on 28 August 2001, because, EXAMPLE 160 (Assay #111; Chondrocyte proliferation assay which demonstrates that the polypeptide encoded by the claimed nucleic acid, induces the proliferation of chondrocytes), which provides a specific and substantial asserted utility or a well established utility for the claimed nucleic acid is disclosed on page 531 of Application no. 09/941,992. However, it does not appear that any of the other prior applications disclose this assay. Specifically, it does not appear that PCT/US99/12252 filed on 02 June 1999, in which the current application claims priority to, discloses the Chondrocyte proliferation assay. Accordingly, the subject matter defined in claims 119-138, is afforded an effective filing date of 28 August 2001, which is the filing date of the U.S application No. 09/941,992.

Should the applicant disagree with the examiner's factual determination above, it is incumbent upon the applicant to provide the serial number and specific page number(s) of any parent application filed prior to 09/04/01, which specifically supports the particular claim limitation for each and every claim limitation in all the pending claims

which applicant considers to have been in possession of and fully enabled for prior to 08/28/01.

Specification:

3a. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Information Disclosure Statement:

4a. References A1 and A2, cited on the PTO-1449 form submitted by Applicants on 31 May 2002 have not been considered, because they do not comply with 37 CFR 1.98(a)(2) requirements, since they fail to identify each publication by author and publication date. Applicant is advised that the date of submission of any item of information or any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the IDS, including all "statement" requirements of 37 CFR 1.97(e). See MPEP § 609 C(1).

Claim rejections-35 USC § 112, first paragraph:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5a. Claims 119-123 and 132-134 are rejected under 35 U.S.C. 112, first paragraph, while being enabling for an isolated nucleic acid comprising the nucleotide sequence set forth in SEQ ID NO:421, and encoding the polypeptide of SEQ ID NO:422, said

polypeptide which induces the proliferation of chondrocytes, does not reasonably provide enablement for an isolated nucleic acid having at least 80%, 85%, 90%, 95% or 99% identity to the nucleic acid encoding the polypeptide of SEQ ID NO:422. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention.

The instant claims 119-123, 132-134 are drawn to an isolated nucleic acid that has at least "80%, 85%, 90%, 95% or 99%" identity to the nucleic acid of SEQ ID NO:421, or having at least 80%, 85%, 90%, 95% or 99% to a nucleic acid encoding the polypeptide of SEQ ID NO:422, or all of the nucleic acids that hybridize to a nucleic acid encoding the polypeptide of SEQ ID NO:422, however, instant specification does not teach how to make or use said nucleic acid. Instant specification discloses that the polypeptide of SEQ ID NO:422 encoded by the claimed nucleic acid induces proliferation of chondrocytes, therefore, said polypeptide is expected to be useful for the treatment of various bone and/or cartilage disorders such as, for example, sports injuries and arthritis, (see Example 160, assay 111 on page 531). Therefore, only the full length polypeptide of SEQ ID NO:422 encoded nucleic acid of SEQ ID NO:421 can be used for said treatments, because Applicants have not shown that variants of the polypeptide of SEQ ID NO:422, induce chondrocyte proliferation.

Instant claims 119-123, 132-134 are drawn to a genus of nucleic acids that are defined only by sequence identity. Due to the large quantity of experimentation necessary to determine all the nucleic acids comprising a nucleotide sequence that is at least 80%, 85%, 90%, 95% or 99% identical to the nucleic acid of SEQ ID NO:421, or

those that hybridize to the nucleic acid of SEQ ID NO:421, and to screen for the ones that encode the polypeptide of SEQ ID NO:422, the lack of direction/guidance presented in the specification regarding which variants of the nucleic acid of SEQ ID NO:421 would retain the desired activity, the complex nature of the invention, the absence of working examples directed to variants of the nucleic acid of SEQ ID NO:421, the state of the prior art establishing that biological activity cannot be predicted based on structural similarity, the unpredictability of the effects of mutation on the structure and function of the claimed polypeptide, and the breadth of the claims which fail to recite particular biological activities, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

5b. Claims 119-123, 132-134 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The instant claims 119-123 are drawn to an isolated nucleic acid that shares "80%, 85%, 90%, 95% or 99%" identity to the nucleic acid of SEQ ID NO:421 or to a nucleic that encodes the polypeptide of SEQ ID NO:422, and claims 132-134 are drawn to an isolated nucleic acid which hybridize to a nucleic acid encoding a specific polypeptide. However, the instant specification only describes the structure of the nucleic acid of SEQ ID NO:421, and therefore, conception is not achieved until reduction to practice has occurred. Adequate written description requires more than a

mere statement that it is part of the invention. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity or hybridizing language. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. Vas-cath Inc. v. Mahurkar, 19 USPQ2d I 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." (See Vas-cath at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993)

and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2II 1016. Therefore, only the isolated nucleic acid set forth in SEQ ID NO: 115, but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph.

Therefore, only the isolated the nucleic acid of SEQ ID NO:421, encoding the polypeptide set forth in SEQ ID NO: 422, but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph.

Claim rejections-35 USC § 112, second paragraph:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 119-124 and 128, 132, are rejected under 35 U.S.C. 1 12, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6a. Claims 119-124, 128 and 132 recite ".....the extracellular domain lacking its associated signal sequence....", which renders the claims indefinite because the signal sequence is not generally considered to be part of an extracellular domain, as signal sequences are cleaved from said domains in the process of secretion from the cell. Appropriate correction is required.

Claim Rejections - 35 U.S.C. §102(b):

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7a. Claims 119-138 are rejected under U.S.C. § 102 (b) as being anticipated by Ashkenazi et al (WO200032221; published 08 June 2000).

Ashkenazi et al disclose an isolated nucleic acid that shares 100% homology to the nucleic acid of SEQ ID NO:421 and an isolated polypeptide that shares 100% homology to the polypeptide of SEQ ID NO:422 of the instant application, a vector comprising said nucleic acid, and a host cell comprising said vector. See attached copies of the comparison of SEQ ID NO:421 and SEQ DI NO:422, of the instant invention and the sequence of the reference (SEQUENCE COMPARISON 'A and B", respectively). The nucleic acid disclosed by Ashkenazi et al encodes an isolated polypeptide that lacks its signal sequence. Ashkenazi et al also disclose an isolated nucleic acid that encodes the extracellular domain, (see claims).

Instant claims 119-138 are drawn to an isolated nucleic acid comprising the nucleotide sequence set forth in SEQ ID NO:421, encodes the polypeptide of SEQ ID NO:422, or encoding said polypeptide lacking its signal sequence, or encoding the extracellular domain of the polypeptide of SEQ ID NO:422. Therefore, the Ashkenazi et al reference meets all the limitations recited in claims 119-138, anticipating said claims, in the absence of any evidence to the contrary.

7b. Claims 119-125, 127, 129-137 are rejected under U.S.C. § 102 (b) as being anticipated by Walker et al (WO200029574; published 25 May 2000).

Walker et al disclose an isolated polypeptide that shares 100% homology to the polypeptide of SEQ ID NO:422 and the nucleic acid encoding said polypeptide, a vector comprising said nucleic acid and a host cell comprising said vector. See attached copies of the comparison of SEQ ID NO:422 of the instant invention and the sequence of the reference (SEQUENCE COMPARISON 'C').

Instant claims 119-125 and 130-137 are drawn to an isolated nucleic acid comprising the nucleotide sequence of SEQ ID NO:421, encoding the polypeptide having SEQ ID NO:422, a vector comprising said nucleic acid and a host cell comprising said vector. Therefore, the Walker et al reference meets all the limitations recited in claims 119-125, 130-137, anticipating said claims, in the absence of any evidence to the contrary.

Conclusion:

8. No claim is allowed.

Advisory Information:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fozia M Hamud whose telephone number is (571) 272-0884. The examiner can normally be reached on Monday, Thursday-Friday, 6:00 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Fozia Hamud
Patent Examiner
Art Unit 1647
15 October 2004

JANET ANDRES
PRIMARY EXAMINER

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Db        1 CGGCTCGAGTGCAGCTGTGGGGAGATTTCAGTGCATTGCCTCCCCTGGGTGCTCTTCATC 60
Qy       61 TTGGATTTGAAAGTTGAGAGCAGCATGTTTTGCCCACTGAAACTCATCCTGCTGCCAGTG 120
Db       61 TTGGATTTGAAAGTTGAGAGCAGCATGTTTTGCCCACTGAAACTCATCCTGCTGCCAGTG 120
Qy      121 TTACTGGATTATTCCTTGGGCCTGAATGACTTGAATGTTTCCCCGCCTGAGCTAACAGTC 180
Db      121 TTACTGGATTATTCCTTGGGCCTGAATGACTTGAATGTTTCCCCGCCTGAGCTAACAGTC 180
Qy      181 CATGTGGGTGATTCAGCTCTGATGGGATGTGTTTTCCAGAGCACAGAAGACAAATGTATA 240
Db      181 CATGTGGGTGATTCAGCTCTGATGGGATGTGTTTTCCAGAGCACAGAAGACAAATGTATA 240
Qy      241 TTCAAGATAGACTGGACTCTGTCACCAGGAGAGCACGCCAAGGACGAATATGTGCTATAC 300
Db      241 TTCAAGATAGACTGGACTCTGTCACCAGGAGAGCACGCCAAGGACGAATATGTGCTATAC 300
Qy      301 TATTACTCCAATCTCAGTGTGCCTATTGGGCGCTTCCAGAACCGCGTACACTTGATGGGG 360
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Db      421 ACCTATATCTGTGAAATCCGCCTCAAAGGGGAGAGCCAGGTGTTCAAGAAGGCGGTGGTA 480
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Db      481 CTGCATGTGCTTCCAGAGGAGCCCAAAGAGCTCATGGTCCATGTGGGTGGATTGATTCAG 540
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Db      601 TCAGGACGGCGCGCAAAGGAGGAGATTGTATTTCGTTACTACCACAAACTCAGGATGTCT 660
Qy      661 GTGGAGTACTCCCAGAGCTGGGGCCACTTCCAGAATCGTGTGAACCTGGTGGGGGACATT 720
Db      661 GTGGAGTACTCCCAGAGCTGGGGCCACTTCCAGAATCGTGTGAACCTGGTGGGGGACATT 720
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Qy      781 ACCTGCAGTATCCACCTAGGGAACCTGGTGTTCAAGAAAACCATTGTGCTGCATGTCAGC 840
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Db      841 CCGGAAGAGCCTCGAACACTGGTGACCCCGGCAGCCCTGAGGCCTCTGGTCTTGGGTGGT 900
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Db      901 AATCAGTTGGTGATCATTGTGGGAATTGTCTGTGCCACAATCCTGCTGCTCCCTGTTCTG 960
Qy      961 ATATTGATCGTGAAGAAGACCTGTGGAAATAAGAGTTCAGTGAATTCTACAGTCTTGGTG 1020
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Db     1021 AAGAACACGAAGAAGACTAATCCAGAGATAAAAGAAAAACCCTGCCATTTTGAAAGATGT 1080
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Qy     1321 TGTGTCCTGGGCCACTCTACCAGTGATTTCAGACTCCCGCTCTCCCAGCTGTCCTCCTGT 1380
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Qy     1381 CTCATTGTTTGGTCAATACACTGAAGATGGAGAATTTGGAGCCTGGCAGAGAGACTGGAC 1440
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Db     1441 AGCTCTGGAGGAACAGGCCTGCTGAGGGGAGGGGAGCATGGACTTGGCCTCTGGAGTGGG 1500
Qy     1501 ACACTGGCCCTGGGAACCAGGCTGAGCTGAGTGGCCTCAAACCCCCCGTTGGATCAGACC 1560
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Qy     1561 CTCCTGTGGGCAGGGTTCTTAGTGGATGAGTTACTGGGAAGAATCAGAGATAAAAACCAA 1620
Db     1561 CTCCTGTGGGCAGGGTTCTTAGTGGATGAGTTACTGGGAAGAATCAGAGATAAAAACCAA 1620
Qy     1621 CCCAAATCAA 1630
Db     1621 CCCAAATCAA 1630
```

Sequence Comparison A

RESULT 2
AAA77683
ID AAA77683 standard; cDNA; 1630 BP.
XX
AC AAA77683;
XX
DT 07-NOV-2000 (first entry)
XX
DE Human PRO1387 cDNA sequence SEQ ID NO:219.
XX
KW Human; PRO; promotion; inhibition; angiogenesis; cardiovascularisation;
KW diagnosis; trauma; wound; cancer; atherosclerosis; cardiac hypertrophy;
KW angiogenic; proliferative; cardiant; cardiovascular; antiatherosclerotic;
KW cytostatic; gene therapy; vaccine; ss.
XX
OS Homo sapiens.
XX
PN WO200032221-A2.
XX
PD 08-JUN-2000.
XX
PF 30-NOV-1999; 99WO-US028313.
XX
PR 01-DEC-1998; 98WO-US025108.
PR 16-DEC-1998; 98US-0112850P.
PR 12-JAN-1999; 99US-0115554P.
PR 08-MAR-1999; 99WO-US005028.
PR 12-MAR-1999; 99US-0123957P.
PR 28-APR-1999; 99US-0131445P.
PR 14-MAY-1999; 99US-0134287P.
PR 02-JUN-1999; 99WO-US012252.
PR 23-JUN-1999; 99US-0141037P.
PR 20-JUL-1999; 99US-0144758P.
PR 26-JUL-1999; 99US-0145698P.

Sequence Comparison 'A'

PR 01-SEP-1999; 99WO-US020111.
PR 08-SEP-1999; 99WO-US020594.
PR 13-SEP-1999; 99WO-US020944.
PR 15-SEP-1999; 99WO-US021090.
PR 15-SEP-1999; 99WO-US021547.
PR 05-OCT-1999; 99WO-US023089.
PR 29-OCT-1999; 99US-0162506P.
XX
PA (GETH) GENENTECH INC.
XX
PI Ashkenazi AJ, Baker KP, Ferrara N, Gerber H, Hillan KJ;
PI Goddard A, Godowski PJ, Gurney AL, Klein RD, Kuo SS, Paoni NF;
PI Smith V, Watanabe CK, Williams PM, Wood WI;
XX
DR WPI; 2000-412154/35.
DR P-PSDB; AAB24433.
XX
PT Nucleic acids encoding PRO polypeptides useful for preventing, diagnosing
PT and treating diagnosing a cardiovascular, endothelial or angiogenic
PT disorders in mammals.
XX
PS Claim 61; Fig 91; 315pp; English.
XX
CC The present invention describes nucleic acids encoding PRO polypeptides
CC useful for preventing, diagnosing and treating diagnosing a
CC cardiovascular, endothelial or angiogenic disorder in mammals by
CC modulating cell proliferation, angiogenesis and cardiovascularisation,
CC and for identifying agonists and antagonists of these processes. The
CC nucleic acids and the proteins they encode may be used in the prevention,
CC treatment and diagnosis of diseases associated with inappropriate PRO
CC expression such as cardiovascular, endothelial or angiogenic disorders in
CC mammals (e.g. atherosclerosis, cancers and cardiac hypertrophy). For
CC example, the nucleic acids (NCs) and vectors containing them and the PRO
CC polypeptide may be used to treat disorders associated with decreased PRO
CC expression. AAA77510 to AAA77721 and AAB24388 to AAB24435 represent
CC nucleotide and protein sequences used in the exemplification of the
CC present invention
XX
SQ Sequence 1630 BP; 425 A; 369 C; 452 G; 384 T; 0 U; 0 Other;

Query Match 100.0%; Score 1630; DB 3; Length 1630;
Best Local Similarity 100.0%; Pred. No. 0;
Matches 1630; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

```
Qy          1 CGGCTCGAGTGCAGCTGTGGGGAGATTTCAGTGCATTGCCTCCCCTGGGTGCTCTTCATC 60
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Qy         61 TTGGATTTGAAAGTTGAGAGCAGCATGTTTTGCCCACTGAAACTCATCCTGCTGCCAGTG 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Qy        121 TTACTGGATTATTCCTTGGGCCTGAATGACTTGAATGTTTCCCCGCCTGAGCTAACAGTC 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Qy        181 CATGTGGGTGATTCAGCTCTGATGGGATGTGTTTTCCAGAGCACAGAAGACAAATGTATA 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Qy        241 TTCAAGATAGACTGGACTCTGTCACCAGGAGAGCACGCCAAGGACGAATATGTGCTATAC 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 TTCAAGATAGACTGGACTCTGTCACCAGGAGAGCACGCCAAGGACGAATATGTGCTATAC 300

Qy        301 TATTACTCCAATCTCAGTGTGCCTATTGGGCGCTTCCAGAACCGCGTACACTTGATGGGG 360
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Db        301 TATTACTCCAATCTCAGTGTGCCTATTGGGCGCTTCCAGAACCGCGTACACTTGATGGGG 360

Qy        361 GACATCTTATGCAATGATGGCTCTCTCCTGCTCCAAGATGTGCAAGAGGCTGACCAGGGA 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        361 GACATCTTATGCAATGATGGCTCTCTCCTGCTCCAAGATGTGCAAGAGGCTGACCAGGGA 420

Qy        421 ACCTATATCTGTGAAATCCGCCTCAAAGGGGAGAGCCAGGTGTTCAAGAAGGCGGTGGTA 480
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        421 ACCTATATCTGTGAAATCCGCCTCAAAGGGGAGAGCCAGGTGTTCAAGAAGGCGGTGGTA 480

Qy        481 CTGCATGTGCTTCCAGAGGAGCCCAAAGAGCTCATGGTCCATGTGGGTGGATTGATTCAG 540
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        481 CTGCATGTGCTTCCAGAGGAGCCCAAAGAGCTCATGGTCCATGTGGGTGGATTGATTCAG 540

Qy        541 ATGGGATGTGTTTTCCAGAGCACAGAAGTGAAACACGTGACCAAGGTAGAATGGATATTT 600
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        541 ATGGGATGTGTTTTCCAGAGCACAGAAGTGAAACACGTGACCAAGGTAGAATGGATATTT 600

Qy        601 TCAGGACGGCGCGCAAAGGAGGAGATTGTATTTCGTTACTACCACAAACTCAGGATGTCT 660
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        601 TCAGGACGGCGCGCAAAGGAGGAGATTGTATTTCGTTACTACCACAAACTCAGGATGTCT 660

Qy        661 GTGGAGTACTCCCAGAGCTGGGGCCACTTCCAGAATCGTGTGAACCTGGTGGGGGACATT 720
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        661 GTGGAGTACTCCCAGAGCTGGGGCCACTTCCAGAATCGTGTGAACCTGGTGGGGGACATT 720

Qy        721 TTCCGCAATGACGGTTCCATCATGCTTCAAGGAGTGAGGGAGTCAGATGGAGGAAACTAC 780
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        721 TTCCGCAATGACGGTTCCATCATGCTTCAAGGAGTGAGGGAGTCAGATGGAGGAAACTAC 780

Qy        781 ACCTGCAGTATCCACCTAGGGAACCTGGTGTTCAAGAAAACCATTGTGCTGCATGTCAGC 840
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        781 ACCTGCAGTATCCACCTAGGGAACCTGGTGTTCAAGAAAACCATTGTGCTGCATGTCAGC 840

Qy        841 CCGGAAGAGCCTCGAACACTGGTGACCCCGGCAGCCCTGAGGCCTCTGGTCTTGGGTGGT 900
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        841 CCGGAAGAGCCTCGAACACTGGTGACCCCGGCAGCCCTGAGGCCTCTGGTCTTGGGTGGT 900

Qy        901 AATCAGTTGGTGATCATTGTGGGAATTGTCTGTGCCACAATCCTGCTGCTCCCTGTTCTG 960
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        901 AATCAGTTGGTGATCATTGTGGGAATTGTCTGTGCCACAATCCTGCTGCTCCCTGTTCTG 960

Qy        961 ATATTGATCGTGAAGAAGACCTGTGGAAATAAGAGTTCAGTGAATTCTACAGTCTTGGTG 1020
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        961 ATATTGATCGTGAAGAAGACCTGTGGAAATAAGAGTTCAGTGAATTCTACAGTCTTGGTG 1020

Qy       1021 AAGAACACGAAGAAGACTAATCCAGAGATAAAAGAAAAACCCTGCCATTTTGAAAGATGT 1080
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1021 AAGAACACGAAGAAGACTAATCCAGAGATAAAAGAAAAACCCTGCCATTTTGAAAGATGT 1080

Qy       1081 GAAGGGGAGAAACACATTTACTCCCCAATAATTGTACGGGAGGTGATCGAGGAAGAAGAA 1140
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1081 GAAGGGGAGAAACACATTTACTCCCCAATAATTGTACGGGAGGTGATCGAGGAAGAAGAA 1140

Qy       1141 CCAAGTGAAAAATCAGAGGCCACCTACATGACCATGCACCCAGTTTGGCCTTCTCTGAGG 1200
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1141 CCAAGTGAAAAATCAGAGGCCACCTACATGACCATGCACCCAGTTTGGCCTTCTCTGAGG 1200

Qy       1201 TCAGATCGGAACAACTCACTTGAAAAAAAGTCAGGTGGGGGAATGCCAAAAACACAGCAA 1260
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1201 TCAGATCGGAACAACTCACTTGAAAAAAAGTCAGGTGGGGGAATGCCAAAAACACAGCAA 1260

Qy       1261 GCCTTTTGAGAAGAATGGAGAGTCCCTTCATCTCAGCAGCGGTGGAGACTCTCTCCTGTG 1320
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1261 GCCTTTTGAGAAGAATGGAGAGTCCCTTCATCTCAGCAGCGGTGGAGACTCTCTCCTGTG 1320

Qy       1321 TGTGTCCTGGGCCACTCTACCAGTGATTTCAGACTCCCGCTCTCCCAGCTGTCCTCCTGT 1380
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1321 TGTGTCCTGGGCCACTCTACCAGTGATTTCAGACTCCCGCTCTCCCAGCTGTCCTCCTGT 1380

Qy       1381 CTCATTGTTTGGTCAATACACTGAAGATGGAGAATTTGGAGCCTGGCAGAGAGACTGGAC 1440
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1381 CTCATTGTTTGGTCAATACACTGAAGATGGAGAATTTGGAGCCTGGCAGAGAGACTGGAC 1440

Qy       1441 AGCTCTGGAGGAACAGGCCTGCTGAGGGGAGGGGAGCATGGACTTGGCCTCTGGAGTGGG 1500
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1441 AGCTCTGGAGGAACAGGCCTGCTGAGGGGAGGGGAGCATGGACTTGGCCTCTGGAGTGGG 1500

Qy       1501 ACACTGGCCCTGGGAACCAGGCTGAGCTGAGTGGCCTCAAACCCCCCGTTGGATCAGACC 1560
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Sequence comparison B'

PR 13-SEP-1999; 99WO-US020944.
PR 15-SEP-1999; 99WO-US021090.
PR 15-SEP-1999; 99WO-US021547.
PR 05-OCT-1999; 99WO-US023089.
PR 29-OCT-1999; 99US-0162506P.
XX
PA (GETH) GENENTECH INC.
XX
PI Ashkenazi AJ, Baker KP, Ferrara N, Gerber H, Hillan KJ;
PI Goddard A, Godowski PJ, Gurney AL, Klein RD, Kuo SS, Paoni NF;
PI Smith V, Watanabe CK, Williams PM, Wood WI;
XX
DR WPI; 2000-412154/35.
DR N-PSDB; AAA77683.
XX
PT Nucleic acids encoding PRO polypeptides useful for preventing, diagnosing
PT and treating diagnosing a cardiovascular, endothelial or angiogenic
PT disorders in mammals.
XX
PS Claim 72; Fig 92; 315pp; English.
XX
CC The present invention describes nucleic acids encoding PRO polypeptides
CC useful for preventing, diagnosing and treating diagnosing a
CC cardiovascular, endothelial or angiogenic disorder in mammals by
CC modulating cell proliferation, angiogenesis and cardiovascularisation,
CC and for identifying agonists and antagonists of these processes. The
CC nucleic acids and the proteins they encode may be used in the prevention,
CC treatment and diagnosis of diseases associated with inappropriate PRO
CC expression such as cardiovascular, endothelial or angiogenic disorders in
CC mammals (e.g. atherosclerosis, cancers and cardiac hypertrophy). For
CC example, the nucleic acids (NCs) and vectors containing them and the PRO
CC polypeptide may be used to treat disorders associated with decreased PRO
CC expression. AAA77510 to AAA77721 and AAB24388 to AAB24435 represent
CC nucleotide and protein sequences used in the exemplification of the
CC present invention
XX
SQ Sequence 394 AA;

Query Match 100.0%; Score 2067; DB 3; Length 394;
Best Local Similarity 100.0%; Pred. No. 5.1e-188;
Matches 394; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

```
Qy    1 MFCPLKLILLPVLLDYSLGLNDLNVSPPELTVHVGDSALMGCVFQSTEDKCIFKIDWTLS 60
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    1 MFCPLKLILLPVLLDYSLGLNDLNVSPPELTVHVGDSALMGCVFQSTEDKCIFKIDWTLS 60

Qy   61 PGEHAKDEYVLYYYSNLSVPIGRFQNRVHLMGDILCNDGSLLLQDVQEADQGTYICEIRL 120
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db   61 PGEHAKDEYVLYYYSNLSVPIGRFQNRVHLMGDILCNDGSLLLQDVQEADQGTYICEIRL 120

Qy  121 KGESQVFKKAVVLHVLPEEPKELMVHVGGLIQMGCVFQSTEVKHVTKVEWIFSGRRAKEE 180
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db  121 KGESQVFKKAVVLHVLPEEPKELMVHVGGLIQMGCVFQSTEVKHVTKVEWIFSGRRAKEE 180

Qy  181 IVFRYYHKLRMSVEYSQSWGHFQNRVNLVGDIFRNDGSIMLQGVRESDGGNYTCSIHLGN 240
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db  181 IVFRYYHKLRMSVEYSQSWGHFQNRVNLVGDIFRNDGSIMLQGVRESDGGNYTCSIHLGN 240

Qy  241 LVFKKTIVLHVSPEEPRTLVTPAALRPLVLGGNQLVIIVGIVCATILLLPVLILIVKKTC 300
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db  241 LVFKKTIVLHVSPEEPRTLVTPAALRPLVLGGNQLVIIVGIVCATILLLPVLILIVKKTC 300

Qy  301 GNKSSVNSTVLVKNTKKTNPEIKEKPCHFERCEGEKHIYSPIIVREVIEEEEPSEKSEAT 360
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db  301 GNKSSVNSTVLVKNTKKTNPEIKEKPCHFERCEGEKHIYSPIIVREVIEEEEPSEKSEAT 360

Qy  361 YMTMHPVWPSLRSDRNNSLEKKSGGGMPKTQQAF 394
          ||||||||||||||||||||||||||||||||||
Db  361 YMTMHPVWPSLRSDRNNSLEKKSGGGMPKTQQAF 394
```

RESULT 5
AAU12431

ID AAU12431 standard; protein; 394 AA.
XX
AC AAU12431;
XX
DT 24-OCT-2001 (first entry)
XX
DE Human PRO1387 polypeptide sequence.
XX
KW Human secretory and transmembrane; PRO; mammalian; cancer; lung; breast;
KW prostate; cervical; tumour necrosis factor-alpha; TNF-alpha; cartilage;
KW ear; proliferation; glucose; free fatty acid; skeletal muscle; adipocyte;
KW A-peptide; factor VIIA; gene therapy.
XX
OS Homo sapiens.
XX
PN WO200140466-A2.
XX
PD 07-JUN-2001.
XX
PF 01-DEC-2000; 2000WO-US032678.
XX
PR 01-DEC-1999; 99WO-US028301.
PR 01-DEC-1999; 99WO-US028634.
PR 02-DEC-1999; 99WO-US028551.
PR 02-DEC-1999; 99WO-US028564.
PR 02-DEC-1999; 99WO-US028565.
PR 09-DEC-1999; 99US-0170262P.
PR 16-DEC-1999; 99WO-US030095.
PR 20-DEC-1999; 99WO-US030911.
PR 20-DEC-1999; 99WO-US030999.
PR 30-DEC-1999; 99WO-US031243.
PR 30-DEC-1999; 99WO-US031274.
PR 05-JAN-2000; 2000WO-US000219.
PR 06-JAN-2000; 2000WO-US000277.
PR 06-JAN-2000; 2000WO-US000376.
PR 11-FEB-2000; 2000WO-US003565.
PR 18-FEB-2000; 2000WO-US004341.
PR 18-FEB-2000; 2000WO-US004342.
PR 22-FEB-2000; 2000WO-US004414.
PR 24-FEB-2000; 2000WO-US004914.
PR 24-FEB-2000; 2000WO-US005004.
PR 01-MAR-2000; 2000WO-US005601.
PR 02-MAR-2000; 2000WO-US005841.
PR 03-MAR-2000; 2000US-0187202P.
PR 10-MAR-2000; 2000WO-US006319.
PR 15-MAR-2000; 2000WO-US006884.
PR 20-MAR-2000; 2000WO-US007377.
PR 21-MAR-2000; 2000WO-US007532.
PR 30-MAR-2000; 2000WO-US008439.
PR 17-MAY-2000; 2000WO-US013705.
PR 22-MAY-2000; 2000WO-US014042.
PR 30-MAY-2000; 2000WO-US014941.
PR 02-JUN-2000; 2000WO-US015264.
PR 05-JUN-2000; 2000US-0209832P.
PR 28-JUL-2000; 2000WO-US020710.
PR 11-AUG-2000; 2000WO-US022031.
PR 23-AUG-2000; 2000WO-US023522.
PR 24-AUG-2000; 2000WO-US023328.
PR 08-NOV-2000; 2000WO-US030952.
PR 10-NOV-2000; 2000WO-US030873.
XX
PA (GETH) GENENTECH INC.
XX
PI Baker KP, Beresini M, Deforge L, Desnoyers L, Filvaroff E, Gao W;
PI Gerritsen ME, Goddard A, Godowski PJ, Gurney AL, Sherwood S;
PI Smith V, Stewart TA, Tumas D, Watanabe CK, Wood WI, Zhang Z;
XX
DR WPI; 2001-408281/43.
DR N-PSDB; AAS21503.
XX
PT Isolated , secretory and transmembrane PRO polypeptide used to detect
PT other PRO polypeptides, link bioactive molecules to cells expressing PRO
PT polypeptides, and detect the presence of mammalian tumors e.g. lung,

Sequence Comparison 'C'

```
Db        61 PGEHAKDEYVLYYYSNLSVPIGRFQNRVHLMGDILCNDGSLLLQDVQEADQGTYICEIRL 120

Qy       121 KGESQVFKKAVVLHVLPEEPKELMVHVGGLIQMGCVFQSTEVKHVTKVEWIFSGRRAKEE 180
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       121 KGESQVFKKAVVLHVLPEEPKELMVHVGGLIQMGCVFQSTEVKHVTKVEWIFSGRRAKEE 180

Qy       181 IVFRYYHKLRMSVEYSQSWGHFQNRVNLVGDIFRNDGSIMLQGVRESDGGNYTCSIHLGN 240
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       181 IVFRYYHKLRMSVEYSQSWGHFQNRVNLVGDIFRNDGSIMLQGVRESDGGNYTCSIHLGN 240

Qy       241 LVFKKTIVLHVSPEEPRTLVTPAALRPLVLGGNQLVIIVGIVCATILLLPVLILIVKKTC 300
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       241 LVFKKTIVLHVSPEEPRTLVTPAALRPLVLGGNQLVIIVGIVCATILLLPVLILIVKKTC 300

Qy       301 GNKSSVNSTVLVKNTKKTNPEIKEKPCHFERCEGEKHIYSPIIVREVIEEEEPSEKSEAT 360
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       301 GNKSSVNSTVLVKNTKKTNPEIKEKPCHFERCEGEKHIYSPIIVREVIEEEEPSEKSEAT 360

Qy       361 YMTMHPVWPSLRSDRNNSLEKKSGGGMPKTQQAF 394
             |||||||||||||||||||||||||||||||||||
Db       361 YMTMHPVWPSLRSDRNNSLEKKSGGGMPKTQQAF 394
```

Sequence Comparison 'C'

```
RESULT 3
AAY94452
ID   AAY94452 standard; protein; 394 AA.
XX
AC   AAY94452;
XX
DT   11-SEP-2000  (first entry)
XX
DE   Human inflammation associated protein #11.
XX
KW   Inflammation; rheumatoid arthritis; Crohn's disease; asthma;
KW   multiple sclerosis; allergy; AIDS; diabetes mellitus antiinflammatory;
KW   gene therapy; human.
XX
OS   Homo sapiens.
XX
PN   WO200029574-A2.
XX
PD   25-MAY-2000.
XX
PF   04-NOV-1999;   99WO-US026234.
XX
PR   18-NOV-1998;   98US-00195292.
XX
PA   (INCY-) INCYTE PHARM INC.
XX
PI   Walker MG,  Volkmuth W,  Klingler TM;
XX
DR   WPI; 2000-387787/33.
DR   N-PSDB; AAA27133.
XX
PT   New human inflammation-associated polypeptide useful for diagnosis,
PT   prevention and treatment of inflammatory diseases comprises product of
PT   gene coexpressed with e.g. CD16, L-selectin and IP-30.
XX
PS   Claim 4; Page 42-43; 43pp; English.
XX
CC   Eleven novel inflammation-associated genes have been identified in cDNA
CC   libraries from various tissues. The genes were selected according to
CC   their coexpression with the known inflammation genes, CD16, L-selectin,
CC   Src-like adapter protein, IP-30, superoxidase homoenzyme subunits, alpha-
CC   1-antitrypsin, C1q-A, 5-lipoxygenase activating protein and SRC family
CC   tyrosine kinase. The novel polynucleotides may be used in hybridization
CC   assays to diagnose a disease or condition associated with altered
CC   expression of the inflammation genes. Antibodies against the genes may be
CC   useful in compositions for the diagnosis and treatment of such diseases
CC   associated with inflammation including rheumatoid arthritis, Crohn's
CC   disease, multiple sclerosis, AIDS, diabetes mellitus, asthma and allergy.
CC   Additionally the polynucleotides of the invention may be used for gene
CC   therapy. The present sequence is human inflammation associated protein
CC   #11, derived from Incyte Clone 3507924
XX
SQ   Sequence 394 AA;

  Query Match             100.0%;  Score 2067;  DB 3;  Length 394;
  Best Local Similarity   100.0%;  Pred. No. 5.1e-188;
  Matches  394;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy         1 MFCPLKLILLPVLLDYSLGLNDLNVSPPELTVHVGDSALMGCVFQSTEDKCIFKIDWTLS 60
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         1 MFCPLKLILLPVLLDYSLGLNDLNVSPPELTVHVGDSALMGCVFQSTEDKCIFKIDWTLS 60

Qy        61 PGEHAKDEYVLYYYSNLSVPIGRFQNRVHLMGDILCNDGSLLLQDVQEADQGTYICEIRL 120
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        61 PGEHAKDEYVLYYYSNLSVPIGRFQNRVHLMGDILCNDGSLLLQDVQEADQGTYICEIRL 120

Qy       121 KGESQVFKKAVVLHVLPEEPKELMVHVGGLIQMGCVFQSTEVKHVTKVEWIFSGRRAKEE 180
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       121 KGESQVFKKAVVLHVLPEEPKELMVHVGGLIQMGCVFQSTEVKHVTKVEWIFSGRRAKEE 180

Qy       181 IVFRYYHKLRMSVEYSQSWGHFQNRVNLVGDIFRNDGSIMLQGVRESDGGNYTCSIHLGN 240
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       181 IVFRYYHKLRMSVEYSQSWGHFQNRVNLVGDIFRNDGSIMLQGVRESDGGNYTCSIHLGN 240

Qy       241 LVFKKTIVLHVSPEEPRTLVTPAALRPLVLGGNQLVIIVGIVCATILLLPVLILIVKKTC 300
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       241 LVFKKTIVLHVSPEEPRTLVTPAALRPLVLGGNQLVIIVGIVCATILLLPVLILIVKKTC 300

Qy       301 GNKSSVNSTVLVKNTKKTNPEIKEKPCHFERCEGEKHIYSPIIVREVIEEEEPSEKSEAT 360
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       301 GNKSSVNSTVLVKNTKKTNPEIKEKPCHFERCEGEKHIYSPIIVREVIEEEEPSEKSEAT 360

Qy       361 YMTMHPVWPSLRSDRNNSLEKKSGGGMPKTQQAF 394
             |||||||||||||||||||||||||||||||||||
Db       361 YMTMHPVWPSLRSDRNNSLEKKSGGGMPKTQQAF 394
```

Sequence Comparison 'B'

```
RESULT 4
AAB24433
ID   AAB24433 standard; protein; 394 AA.
XX
AC   AAB24433;
XX
DT   07-NOV-2000  (first entry)
XX
DE   Human PRO1387 protein sequence SEQ ID NO:220.
XX
KW   Human; PRO; promotion; inhibition; angiogenesis; cardiovascularisation;
KW   diagnosis; trauma; wound; cancer; atherosclerosis; cardiac hypertrophy;
KW   angiogenic; proliferative; cardiant; cardiovascular; antiatherosclerotic;
KW   cytostatic; gene therapy; vaccine.
XX
OS   Homo sapiens.
XX
PN   WO200032221-A2.
XX
PD   08-JUN-2000.
XX
PF   30-NOV-1999;   99WO-US028313.
XX
PR   01-DEC-1998;   98WO-US025108.
PR   16-DEC-1998;   98US-0112850P.
PR   12-JAN-1999;   99US-0115554P.
PR   08-MAR-1999;   99WO-US005028.
PR   12-MAR-1999;   99US-0123957P.
PR   28-APR-1999;   99US-0131445P.
PR   14-MAY-1999;   99US-0134287P.
PR   02-JUN-1999;   99WO-US012252.
PR   23-JUN-1999;   99US-0141037P.
PR   20-JUL-1999;   99US-0144758P.
PR   26-JUL-1999;   99US-0145698P.
PR   01-SEP-1999;   99WO-US020111.
PR   08-SEP-1999;   99WO-US020594.
```